Genetic Heterogeneity of Sickle Mutations

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The wide spectrum of severity of sickle cell anemia has been a puzzling feature for a long time. The substitution of valine for glutamic acid at position 6 of the abnormal β chain is always the same, and the polymerization and sickling processes are extremely well known. Ecological factors are obviously involved in this variability, including climate, socioeconomic conditions, and medical environment. They can nevertheless not account for all the differences observed. Significant progress has been made in the last few years to evaluate the epistatic effect of other genetic factors, two of which have been thoroughly studied:

The concomitant presence of α -thalassemia is an unlinked epistasis. The most constant effect is a reduction of anemia due to decreased hemolysis. A reduced proportion of very dense cells is also consistently observed. There is no appreciable variation in the level of hemoglobin F. And some major complications, related to vaso-occlusive crises, are not modified [1]. This interaction seems nevertheless to be generally beneficial, at least in the $\alpha\alpha$ -homozygous state. Its age dependency argues for an increased survival of SS patients, and in some populations the α -thalassemia gene frequency is significantly higher in SS patients than it is in controls [2]. Probably still more important is the epistatic effect of linked genes, including the genes located upstream on chromosome 11. Since the initial description of an Hpa I polymorphism 3' to the β gene, many other polymorphic sites have been described spanning the 60 kb of the β gene cluster, and their distribution constitutes specific haplotypes [3]. Three main haplotypes were found linked to the hemoglobin S

gene, which were demonstrated to be geographically segregated in Africa [4]. These three haplotypes also represent 90% of SS patients of Jamaica. Another related haplotype has been described in Eastern Saudi Arabia and in Turkish patients [5] and found similarly in North India [6]. These haplotypes correspond to genetically distinct forms of sickle cell anemia. In Senegalese and Saudi Arabian type, the main characteristic is a higher level of hemoglobin F and a neonatal percentage of G γ chain [7] together with the presence of a specific Xmn I polymorphism 5' to the G γ gene [8]. In the Beninian and the Bantu patients there is a low G expression of the 'adult type' [9]. Nevertheless, the level of hemoglobin F is higher in the second group, the distribution of these levels is quite different, and there is in this latter one (Bantu) a

strong correlation between hemoglobin F and G γ expression not observed anywhere else [10]. From our present knowledge, it appears that both these epistatic effects, α -thalassemia and hemoglobin F, seem to be non-additive.

Beside these two well-studied genetic factors, there must be many others, including for example the genetically determined number of F reticulocytes, or some specific rheological properties.

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